Remarks

Redundancy of Priority Claims in the Specification The applicants have responded to the Examiner's objections to the redundancy of priority claims (p. 2 of the Final Rejection of Oct. 20, 2009) by requesting a deletion of the redundant priority claims on pages 9 and 49 of the Specification.

Rejection of the claims for indefiniteness The Examiner rejected the claims as being indefinite under 35 USC 112, second paragraph. More specifically the Examiner states that the limitation *"wherein N is less than maximal, whereby the number and distribution of known markers in the neighborhood of the CL-F region make it possible for N to be a greater value"* renders independent claim 91 indefinite; see p. 9 of the Final Rejection. The applicants have responded by amending claim 91 and deleting this limitation.

Rejection of the claims for lack of Priority The Examiner rejected the claims based on failing to meet the requirements for priority under 35 USC 119(e), 120, 121 or 365(c), see p. 2 of the Final Rejection. More specifically this rejection was based on a failure of the priority documents (e.g., PCT/US99/04376 and 09/947,768) to meet the requirements of the first paragraph of 35 USC 112, including lack of support in these priority documents. The applicants now respectfully point out that <u>detailed support</u> for each limitation in claim 91 (in the PCT parent, PCT/US99/04376 & provisional priority application 60/076102) was cited on pp. 52-57 of the Amendment/Response of March 10, 2009, including for the limitation(s) cited by the Examiner in the Final Rejection. The applicants will not repeat those detailed remarks verbatim here. The applicants respectfully request that the Examiner read those detailed remarks carefully. Other detailed support for each limitation in <u>all</u> the claims is also cited in the Remarks of 3/10/2009. The applicants respectfully point out that support under 112, 1st paragraph need not be verbatim or "ipsis verbis."

It should be noted as stated on 3/10/2009, that the whereby clauses in claim 91 are not true limitations, but follow from the other limitations in the claim. The Examiner has also misquoted the claim limitation *"wherein the length of the segment of the segment-subrange is greater than or equal to the length of human chromosome 21, whereby the length of the segment is greater than or equal to about 47 million base pairs"* in the Final Rejection. The Examiner has substituted the word "whereby" for the first (underlined) "wherein" in the limitation quoted above in the Final Rejection. In addition, support for the limitation(s) & clauses(s) cited in the Final Rejection, including those regarding chromosome 21 and 47 million base pairs, are discussed on pp. 54-57 of the Amend./Response of 3/10/2009.

The applicants have also responded to this point of rejection below, by rebutting the Examiner's contention that the claims fail to meet the requirements of the first paragraph of 35 USC 112. The parts of the instant Specification that are cited have identical (or essentially identical) passages in the PCT parent, PCT/US99/04376. And the applicants will attempt to cite these PCT passages below in parallel with the citations for the instant Specification in the rebuttal of enablement & WD Req rejections below.

Rejection of the Claims for failure to meet 35 USC 112, 1st paragraph Requirements

The Examiner rejected the claims for failure to meet the requirements 35 USC 112, 1st paragraph, see Final Rejection of Oct. 20, 2009, pp. 3 to 9.

Rebuttal of the Rejection of the claims for lack of Enablement under 35 USC 112, 1st paragraph

The Examiner rejected the claims for *"containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to*

which it pertains, or with which it is most nearly connected, to use the invention;" see top p. 4 of the Final Rejection of Oct. 20, 2009. The applicants respectfully but strongly disagree with this rejection and present the following rebuttal.

Summary of the Rebuttal of the Enablement Rejection

The scope of each claim is fully enabled; the claims are product by process claims and the process limitations that define each claimed invention are fully enabled. The art (at the time of filing) and the instant Specification (and the PCT parent) contain the following enabling teachings.

A) The Specification and art teach a person of ordinary skill in the art how to choose markers that have general CL-F coordinates (chromosomal location and least common allele frequency coordinates) so that the markers N-cover the claimed CL-F regions. These claimed CL-F regions are rectangular segment-subranges. **The applicants illustrate some of this teaching using Diagrams 1 & 2 below on page 45.**

To use the analogy of a chessboard used in the Background of the application(s), conventional 1D techniques (for choosing linkage study markers) essentially place a marker in each of the 8 squares of the first row of the chessboard <u>to achieve one-dimensional closeness</u>. New 2D techniques (for choosing linkage study markers taught by the application) for N-covering segment-subrange(s) essentially place a marker in each of one or more contiguous rows of the chessboard **<u>to achieve two-dimensional closeness</u>**. For example, new 2D techniques essentially place a marker in: (1) all 64 squares of the board, or (2) all 16 squares of the first two rows, or (3) all 24 squares of the first three rows, or (4) all 8 squares of the last row. **<u>Given the high level of skill of ordinary persons in the art, it simply is not reasonable to believe that such highly skilled persons could not think in this new, but simple two-</u>**

dimensional way, when given the teaching in the Specification(s) (including the priority applications).

B) The availability of very large numbers (e.g., thousands and millions) of bi-allelic markers (e.g., SNPs) that could be used for the purpose recited in the claims (N-covering of segment-subranges) was reasonably predictable at the time of filing. Routine type procedures for discovering and identifying these very large numbers of bi-allelic markers (for a population) **without undue experimentation** were known and being used at the time of filing. (Thousands of such markers were also already identified at the time of filing as well.) **Thus the identification of specific bi-allelic markers with specific CL-F coordinates that meet the general CL-F coordinate requirements for N-covering under A) above was possible without undue experimentation at the time of filing.** (Work & experimentation in the art post-filing, e.g., the subsequent discovery of millions of SNPs, has borne out this statement.) **Each of these specific bi-allelic markers also has a specific DNA sequence.**

C) It is a simple and reasonably predictable matter to select complementary oligonucleotides with utility to determine genotype data or sample allele frequency data for each of the two or more specific "covering" markers with known DNA sequences. **Given this predictability, only general knowledge that is well-known in the art is necessary to enable the oligonucleotide selection process claim limitation(s) when the DNA sequences of the covering markers are known.**

In summary then, because of the combination of arguments A), B) & C) above, the applicants submit that the scope of each claim is fully enabled.

More details of the rebuttal of the enablement rejection

Firstly, the applicants respectfully point out that the rejected claims are <u>product by process</u> claims, see pp. 15, 71, & 75 of the Amendment/Response of March 10, 2009. And the applicants respectfully submit that the instant claimed invention(s) are characterized by process limitations. This is an important consideration since an important factor in determining enablement is *"The nature of the invention,"* see MPEP 2164.01(a) Undue Experimentation Factors and p. 6 of the Final Rejection.

Independent claim 91 contains the process limitation *"wherein the set of oligonucleotides is selected for the set's utility to determine genotype data or sample allele frequency data for each of the two or more covering markers."* **And independent claim 91 also contains the process limitation** *"wherein the group of covering markers is chosen so that a CL-F region is N covered to within [x, y] by the covering markers."*

The applicants will now address these process limitations that define the invention. Specifically we first address the limitation regarding choosing bi-allelic "covering" markers to achieve "N-covering" of a CL-F region and second we address the limitation regarding selecting complementary oligonucleotides.

The applicants preface this rebuttal by noting that the MPEP states the specification need only disclose one method for making and using the claimed invention in order to meet the enablement requirement (see MPEP 2164.01(b)). And **the amount of guidance needed from the Specification varies inversely with the amount of knowledge and predictability in the art** (see MPEP 2164.03).

Independent claim 91 contains the N-covering process limitation *"wherein the group of covering markers is chosen so that a CL-F region is N covered to within [x, y] by the covering markers, wherein [x, y] is a two-dimensional distance, wherein x is less than or equal to 1 million base pairs and y is less than or equal*

to 0.2, N is an integer greater than or equal to 1, ...wherein the CL-F region is a segment-subrange." There was a great deal of guidance in the art at the time of filing and in the instant specification (& PCT parent) to allow a person of ordinary skill in the art to practice this limitation without undue experimentation. **As noted in A) above, the Specification (& PCT parent) and art teach a person of ordinary skill in the art how to choose markers that have general CL-F coordinates (chromosomal location and least common allele frequency coordinates) so that the markers N-cover the claimed CL-F regions.** These claimed CL-F regions are rectangular segment-subranges. **The applicants illustrate some of this teaching using Diagrams 1 & 2 below on p. 45.**

As stated by the Examiner, *"The skill of those in the art of ... linkage analysis is high,"* see p. 7 of the Final Rejection. As noted in the Background of the present application, conventional techniques for choosing markers for linkage studies are **<u>essentially one dimensional</u>** and use markers that are spaced approximately evenly along a chromosome, see e.g., p. 3 line 14 to p. 4 line 11 of the present application, 10/037, 718 (p. 3 lines 1 to 32 of the PCT parent). Some specific examples of some average spacing between markers are given, see p. 3 lines 18, 22 and 25 (PCT p. 3 lines 5, 9 & 12). (As is & was known in the art, the inter-marker spacing of 1 cM in the example given on line 25 (line 12 PCT) is equivalent to about 1 million base pairs between markers.)

As is & was well-known in the art of linkage studies, the purpose of spacing markers approximately evenly along a chromosome is to attempt to locate one or more of the markers close (on the chromosome) to a gene or trait-causing polymorphism and to achieve linkage between the trait-causing polymorphism and the one or more close markers, see Background, p. 2 line 8-13 (PCT p. 1 lines 33-38). As is & was well-known in the art, using a small average inter-marker spacing to scan a chromosomal region essentially ensures that the distance (on the chromosome) between one or more of the markers and a trait-causing polymorphism in the region will (on average) be less than or equal to

about half the inter-marker spacing distance. By distributing markers approximately evenly along a chromosome or chromosomal region (or segment) in this conventional way, the chromosome or chromosomal region is "covered" (in a one-dimensional manner) by the markers, see Background of 10/037, 718, p. 3 lines 29-30 (PCT p. 3 lines 16-17).

As was well-known in the conventional art at the time of filing, better coverage is generally achieved with denser marker spacing (less average inter-marker distance along the chromosome); see for example Background p. 3 lines 23-27 (PCT p. 3 lines 10-14). As was well-known, this is because smaller distances between a marker and trait-causing polymorphism are generally associated with higher degrees of linkage, including linkage disequilibrium (LD); see e.g., Background, p. 2 line 8-13 (PCT p. 1 lines 33-38). See also the quote from Cohen (1997) about LD on p. 36 of the Amendment/Response of March 10, 2009 for the present application. Cohen (1997) is a patent reference cited by the Examiner.

As was well-known in the conventional art at the time of filing, bi-allelic markers with the highest heterozygosity, those with most common/least common allele frequencies close to 0.5/0.5, have the highest "information content" from the perspective of the conventional art of linkage analysis. See Background p. 4 line 35 to p. 5 line 11 (PCT p. 4 lines 21 to 34), which cites Kruglyak (<u>The use of a genetic map of biallelic markers in linkage studies.</u> Nature Genetics, September 1997, vol.17, pp. 21-24). This Kruglyak (1997) reference is cited in the Background of the present application, see footnote 4, p. 5 (p. 4 PCT). A copy of this Kruglyak (1997) reference was supplied as Reference F in an Information Disclosure Statement (IDS) filed in November 2000 for parent application 09/623,068.

These concepts of using approximately evenly spaced markers to **(1)** achieve "coverage," "one-dimensional closeness" and possible linkage and **(2)** the

favoring of bi-allelic markers with most common/least common allele frequencies near 0.5/0.5, are & were second nature to persons of ordinary skill in the conventional art of linkage studies. **As stated in MPEP 2164.01 (under the Enablement Requirement) *"A patent need not teach, and preferably omits, what is well known in the art."* But to rebut the enablement rejection (by aiding the Examiner to better understand the conventional art of linkage studies) a simple diagram, Diagram 1, illustrating this approximate spacing of markers and one- dimensional "coverage" is appended to this paper.**

In Diagram 1 the chromosomal location (or position) of each bi-allelic marker in a conventional linkage study is indicated by an "+" sign. Diagram 1 shows six bi-allelic markers that are spaced approximately evenly across a chromosomal segment with the spacing between markers being about 1cM (or about 1 million base pairs). A "P" indicates the chromosomal position of a trait-causing polymorphism whose location is being sought in the linkage study. Diagram 1 shows that the distance on the chromosome between the polymorphism and the two closest markers is less than or equal to about 1cM x 1/2 = about 0.5cM (or about 500 thousand base pairs). **Similarly, each point on the chromosomal segment is within a (chromosomal location) distance of less than or equal to about 0.5cM or 500 thousand base pairs of one or two markers.** Diagram 1 contains no information about the allele frequencies of the bi-allelic markers (or the polymorphism), but the most common/least common allele frequencies of each of these six bi-allelic markers is close to 0.5/0.5. **Diagram 1 thus illustrates a typical conventional choice of bi-allelic markers to scan a chromosomal segment for a conventional linkage study at the time of filing.**

In Diagram 2 (also appended), the same six bi-allelic markers of Diagram 1 are located on a two-dimensional CL-F map that shows both the chromosomal location and least common allele frequency of each marker. **Since these are the same six markers, it is clear that each point on the chromosomal segment is still within a chromosomal location (CL-axis or x-axis) distance of less**

than or equal to about 0.5cM or 500 thousand base pairs of one or two markers.

Similarly, since the markers all have least common allele frequencies close to 0.5, each CL-F point on the map with a higher least common allele frequency coordinate (e.g., ≥ 0.3) is close in terms of frequency distance (along the F-axis or y-axis) to each of the six markers. For example, each CL-F point on the map with a least common allele frequency coordinate ≥ 0.3 is within a frequency distance of 0.2 of each of the six markers. And each CL-F point on the map with a least common allele frequency coordinate ≥ 0.4 is within a frequency distance of 0.1 of each of the six markers.

The above described two-dimensional closeness (in terms of both the CL or x axis and the F or y axis) achieved by the conventional choice of markers means that each point in two example CL-F regions is N-covered to within [x, y]. The two example CL-F regions (that are illustrated on Diagram 2) that are N-covered to within [x, y] are two segment-subranges, rectangular regions on the CL-F map of Diagram 2. The large segment-subrange (dotted line border) is bounded by the chromosomal segment (that is about 5cM long) and the allele frequency subrange 0.3 to 0.5. The smaller segment-subrange (dots and dashes border) is bounded by a slightly smaller chromosomal segment and the allele frequency subrange 0.4 to 0.5. The larger segment subrange is N-covered to within [x, y], wherein N =1 and x is about 0.5 cM or 500 thousands base pairs and y is 0.2. The smaller segment subrange is N-covered to within [x, y], wherein N =1 and x is about 0.5 cM or 500 thousands base pairs and y is 0.1. **Thus, as illustrated by the Diagrams (1 & 2, p. 45), the conventional art gave a great deal of guidance as to the choice of markers needed to N-cover a segment-subrange.**

The guidance in the conventional art and the specification makes it very easy to <u>extrapolate</u> to N-covering other segment-subranges with various

values for N and [x, y]. For example, by using denser marker spacing along a chromosome (as was well-known in the conventional art), higher values of "N" and lower values of "x" are achieved. By using, for example, covering markers with lower least common allele frequencies, as suggested by the Specification (see p. 45 lines 25-28 & Table 2 p. 41; PCT p. 44 lines 25-28 & Table 2 p. 40), segment-subranges that include CL-F points with lower frequency coordinates can also be N-covered. Also for example, by using covering markers with varying lower least common allele frequencies, as suggested by the Specification (see p. 45 lines 25-28; PCT p. 44 lines 25-28), smaller values of "y" can be achieved. As noted in MPEP 2164.03 (Relationship of Predictability of the Art and the Enablement Requirement), *"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to* ***extrapolate*** *the disclosed or known results to the claimed invention."*

The Set/Subset Example in the Specification also describes how to N-cover a very large segment-subrange that is bounded by an entire chromosome and by the subrange (or range) 0 to 0.5. The Set/Subset Example is described on p. 44 line 4 to p. 47 line 32 (or Best Mode Example PCT p. 43 line 4 to p. 46 line 32).

In this Set/Subset Example the chromosome is completely covered by segments (see p. 44 lines 26-27; or Best Mode Example PCT p. 43 lines 26-27). The segments are, for example, 7 –10 cMs, or less than 1 cM, or 250, 000 base pairs in length. Within each segment, there are subsets of (covering) markers, see p. 45 lines 23-24; or PCT p. 44 lines 23-24. Thus each point on the chromosome is within a small (e.g., 10cM, 7cM, 1cM or 250,000 bp) chromosomal distance (along the CL axis or x-axis) of markers.

And each subset of (covering) markers contains only markers having least common allele frequencies that are approximately the same (e.g., about 0.1, 0.2, 0.3, 04. & 0.5), see p. 45 lines 23-28; or PCT p. 44 lines 23-28. The least

common allele frequencies of the markers in each subset differ by no more than 0.15, see p. 46 lines 1-2; or PCT p. 45 lines 1-2. **Thus the Set/Subset Example teaches how to N-cover a very large segment-subrange to within [x, y], where N ≥ 2, x = 10cM, 7cM, 1cM or 250, 000 bp, and y ≤ 0.15**. This section of the Specification also describes how to N-cover smaller segment-subranges that are bounded by a subregion of interest (e.g., chromosomal segment) or smaller frequency subrange, see p. 44 lines 17, 26 & 27 (or PCT p. 43 lines 17, 26 & 27) and p. 47 lines 26-29 (or PCT p. 46 lines 26-29).

<u>IN SUMMARY,</u> as noted in A) above, the Specification (& PCT parent) and art teach a person of ordinary skill in the art how to choose markers that have general CL-F coordinates (chromosomal location and least common allele frequency coordinates) so that the markers N-cover the claimed CL-F regions. These claimed CL-F regions are rectangular segment-subranges.

As described, conventional linkage study techniques have an essentially one-dimensional (1D) perspective for choosing at the time of filing, see Background p. 4 lines 3-11 (PCT p. 3 lines 24-32). The present application teaches a two-dimensional perspective, see e.g., the title, and Background p. 7 lines 17-22 (PCT p. 7 lines 6-11). **The application(s) use the analogy of a chessboard, see Background p. 8 lines 12-16. PCT p. 7 line 38 to p. 8 line 3. Using this analogy (of a chessboard) conventional 1D techniques (for choosing linkage study markers) essentially place a marker in each of the 8 squares of the first row of the chessboard <u>to achieve one-dimensional closeness</u>.**

New 2D techniques (for choosing linkage study markers taught by the application) for N-covering segment-subrange(s) essentially place a marker in each of one or more contiguous rows of the chessboard <u>to achieve two-dimensional closeness</u>. For example, new 2D techniques essentially place a marker in: (1) all 64 squares of the board, or (2) all 16 squares of the first two rows, or (3) all 24 squares of the first three rows, or (4) all 8 squares of the last

row. As stated by the Examiner, *"The skill of those in the art of … linkage analysis is high,"* see p. 7 of the Final Rejection. **It simply is not reasonable to believe that such highly skilled persons of ordinary skill in the art could not think in this new, but simple two-dimensional way when given the teaching in the instant Specification (and PCT parent and provisional priority application 60/076102).**

B) The availability of very large numbers (e.g., thousands and millions) of bi-allelic markers (e.g., SNPs) that could be used for the purpose recited in the claims (N-covering of segment-subranges) was reasonably predictable at the time of filing. Routine type procedures for discovering and identifying these very large numbers of bi-allelic markers (for a population) **without undue experimentation** were known and being used at the time of filing. (Thousands of such markers were also already identified at the time of filing as well.) **Thus the identification of specific bi-allelic markers with specific CL-F coordinates that meet the general CL-F coordinate requirements for N-covering under A) above was possible without undue experimentation at the time of filing.** (Experience in the art post-filing, e.g., the subsequent discovery of millions of SNPs, has borne out this statement.) **Each of these specific bi-allelic markers also has a specific DNA sequence.**

Most of the bi-allelic markers now presently available were not identified by 26 Feb 1998. See for example p. 21 mid right column of Kruglyak (The use of a genetic map of biallelic markers in linkage studies. Nature Genetics, September 1997, vol.17, pp. 21-24) that states *"..classic estimates of more than 1 per 1,000 base pairs, or more than 3 million* [SNPs] *in the genome. To date, more than 1,000 PCR amplifiable SNP markers have been discovered and mapped (D. Wang, pers. comm.)."* It should be noted that 3 million SNPs in the entire genome translates to about 130, 000 SNPs (3 million/23) per human chromosome. (This Kruglyak (1997) reference is cited in the Background of the present application, see footnote 4, p. 5 (PCT p.4). A copy of this Kruglyak (1997) reference was

supplied as Reference F in an Information Disclosure Statement (IDS) filed in November 2000 for parent application 09/623,068.)

Significant efforts were, however, underway using routine type methods to identify SNPs for future use by about 26 Feb 1998. For example, see Abstract of a slide presentation: Wang, D. et al. Toward a third generation genetic map of the human genome based on biallelic polymorphisms. Am. J. Hum. Genet. 59, A3 (1996). The Abstract states that 400 SNPs had been discovered by the authors. See also Kwok, et. al., (Genome Res. 1998 8: 748-754, Overlapping Genomic Sequences: A Treasure Trove of Single- Nucleotide Polymorphisms), this paper describes finding 153 SNPs over a 200.6 kb region. A paper by Kwok, et. al. (Hum Mutat. 1998;12(4):221-5 Single nucleotide polymorphism hunting in cyberspace) describes finding SNPs by computer analysis of data. A Wang reference (Large Scale Identification, Mapping, and Genotyping of Single-Nucleotide Polymorphisms in the Human Genome, Wang, et. al., Science, May 15, 1998, vol 280, pp. 1077-1081) describes finding 3241 candidate SNPs and mapping 2227 of these SNPs (a 500 SNP genotyping chip is also described). This Wang reference is referred to in the present application on p. 35 lines 11-13 (PCT p. 34 lines 11-13) and endnote 9 p. 49 (PCT p. 48). **Copies of the Wang slide presentation Abstract, both Kwok papers and this 1998 Wang reference have been supplied to the Examiner for his convenience with the Amendment/Response of March 10, 2009.**

Thus the identification of specific bi-allelic markers with <u>specific DNA sequences</u> and specific CL-F coordinates that meet the general CL-F coordinate requirements for N-covering under A) above was possible using routine type methods known in the art <u>without undue experimentation</u> at the time of filing.

C) As is known in the art, it is a <u>simple and predictable</u> matter to select an oligonucleotide that is complementary to a marker with a <u>known DNA</u>

sequence. For example, it is simple and predictable to select a complementary oligonucleotide that will hybridize to a marker with a known DNA sequence. Similarly it is simple and reasonably predictable to select complementary oligonucleotides with utility to determine genotype data or sample allele frequency data for each of the two or more "covering" markers with known DNA sequences. **Given this predictability, only general knowledge that is well-known in the art is necessary to enable the oligonucleotide selection process limitation when the DNA sequences of the covering markers are known.**

Such general knowledge is provided in the application. As the Examiner stated in the Final Rejection (bottom p. 4, top p. 5): *"The specification generally describes principles and concepts for using a set of oligonucleotides, technology for genotyping of individuals … for bi-allelic covering markers [See at least p. 21, 22, 32, 35, 36, 37, 39]."* (See PCT p. 20, 21, 31, 34, 35, 36, 38.) Also, as stated by the Examiner, *"The skill of those in the art of genotyping and linkage analysis is high,"* see p. 7 of the Final Rejection. **Thus, when the DNA sequences of the covering markers are known, the oligonucleotide selection process claim limitation is clearly enabled. As explained above, the choosing of a group of covering markers that N-cover a CL-F region and the determination of the DNA sequences of such covering markers is enabled. As the applicants have show above, this determination of the DNA sequences of covering markers that N-cover a CL-F region does not involve undue experimentation.**

SUMMARY In summary then, because of the combination of arguments A), B) & C), which were made in more detail above, the applicants respectfully submit that it is clear that the scope of each product by process claim is fully enabled.

Rebuttal of the Rejection of the claims for lack of a Written Description under 35 USC 112, 1st paragraph

Summary of the rebuttal of the WD Requirement Rejection

The claims are product by process claims and the process limitations that define each claimed invention are practice-able in a reasonably predictable way. Indeed the applicants have limited the scope of the claims to products produced by the recited process of an equivalent process. **The claims allow the claimed product by process invention(s) to be distinguished from other materials. The claims thus meet the Written Description of 35 USC 112, 1st paragraph.** (More details of the practice-ability of the process limitations of the claimed product by process invention(s) in a reasonably predictable way are also given above under the rebuttal of the Enablement Rejection.)

More details of the rebuttal of the WD Requirement Rejection

This gist of the rejection for failure to meet the WD Requirement is that *"However, the specification does not provide any disclosure of oligonucleotide compositions (e.g. specific SEQ ID numbers) obtained according to limitations set forth in the claims (See claim 91),"* see p. 9 of the Final Rejection. The applicants respectfully submit that such a disclosure of specific structure is unnecessary to meet the WD Req. of 112. **The applicants respectfully point out that the rejected product claims are product by process claims, see pp. 15, 71, & 75 of the Amendment/Response of March 10, 2009.** Moreover the applicants have limited the scope of the claims to products produced by the recited process or an equivalent process, see p. 71 of the Amend./Resp. of 3/10/2009.

Regarding product by process claims and the WD Req., MPEP 2163 II A. 3. (a) i) states in part (emphasis added): *"In contrast, for inventions in emerging and*

unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession. For example, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim other than a ***product-by-process claim****. See, e.g., Fiers v. Revel, 984 F.2d at 1169, 25 USPQ2d at 1605; Amgen, 927 F.2d at 1206, 18 USPQ2d at 1021. Where the process has actually been used to produce the product, the written description requirement for a product-by-process claim is clearly satisfied; however, the requirement may not be satisfied where it is not clear that the acts set forth in the specification can be performed, or that the product is produced by that process."*

Thus, as stated in *Fiers,* the standard for meeting the WD Req. is different for a product by process than for a product per se. And exhaustive, specific disclosure of details of structure (e.g., specific SEQ ID numbers) is not necessarily needed to meet the WD Req. for a product by process claim.

The applicants respectfully submit that the instant claimed invention is characterized by factors (process limitations) that were & are practice-able in a reasonably predictable way. The applicants will now discuss the practice-ability & reasonable predictability of the process limitations that define the claimed invention. **More details of this practice-ability and reasonable predictability are also given above under the rebuttal of the Enablement Rejection.**

Independent claim 91 contains the process limitation *"wherein the group of covering markers is chosen so that a CL-F region is N covered to within [x, y] by the covering markers."* The availability of large numbers of (bi-allelic) markers that could be used for the purpose recited in the claim limitation ("N-covering") was reasonably predictable at the time of filing. It was then known in the art that thousands, even millions, of bi-allelic markers (e.g., SNPs) would likely become

identified and become available for future use in linkage studies. See for example p. 21 mid right column of Kruglyak (The use of a genetic map of biallelic markers in linkage studies. Nature Genetics, September 1997, vol.17, pp. 21-24) that states *"classic estimates of more than 1 per 1,000 base pairs, or more than 3 million* [SNPs] *in the genome."* It should be noted that 3 million SNPs in the entire genome translates to about 130, 000 SNPs (i.e., 3 million/23) per human chromosome. This Kruglyak (1997) reference is cited in the Background of the present application, see footnote 4, p. 5 (p. 4 PCT). A copy of this Kruglyak (1997) reference was supplied as Reference F in an Information Disclosure Statement (IDS) filed in November 2000 for parent application 09/623,068.

Discovery methods were known, and significant discovery efforts were also underway, by about the time of filing of the first priority application to identify such markers (e.g., SNPs) for use in linkage studies. These discovery methods and efforts were discussed previously in the Amendment/Response of March 10, 2009, see bottom p. 72. **And these discovery methods and efforts are also discussed in more detail above under the rebuttal of the Enablement Rejection. Thus the process limitation recited in independent claim 91 regarding N-covering** (*"wherein the group of covering markers is chosen so that a CL-F region is N covered to within [x, y] by the covering markers")* **was practice-able in a reasonably predictable way at the time of filing.**

Independent claim 91 also contains the process limitation *"wherein the set of oligonucleotides is selected for the set's utility to determine genotype data or sample allele frequency data for each of the two or more covering markers."* **The applicants also respectfully submit that this process limitation was also practice-able in a reasonably predictable way at the time of filing.**

As is known in the art, it is a **simple and predictable** matter to select an oligonucleotide that is complementary to a marker with a known DNA sequence. For example, it is simple and predictable to select a complementary

oligonucleotide that will hybridize to a marker with a known DNA sequence. Similarly it is simple and reasonably predictable to select complementary oligonucleotides with utility to determine genotype data or sample allele frequency data for each of the two or more "covering" markers with known DNA sequences. Given this simplicity and predictability of selecting a complementary oligonucleotide, and given (as stated above), that the process limitation reciting N-covering by covering markers was practice-able (in a reasonably predictable way at the time of filing), it follows that the process limitations defining the claimed invention of claim 91 were also practice-able in a reasonably predictable way at the time of filing. **And the claimed invention(s) meet the Written Description Requirement of 35 USC 112, 1st paragraph.**

As the Examiner stated in the Final Rejection (p. 9): *"The specification generally describes principles and concepts for using a set of oligonucleotides, technology for genotyping of individuals … for bi-allelic covering markers [See at least p. 21, 22, 32, 35, 36, 37, 39]."* (See PCT p. 20, 21, 31, 34, 35, 36, 38.) Also, as stated by the Examiner, *"The skill of those in the art of genotyping and linkage analysis is high,"* see p. 7 of the Final Rejection. The applicants respectfully submit that there is therefore enough information in the application to meet the Written Description Requirement. **Again, more details of the practice-ability of the process limitations of the claimed product by process invention in a reasonably predictable way are also given above under the rebuttal of the Enablement Rejection.**

In addition, the applicants respectfully submit that for the reasons stated above, **the claims allow the claimed product by process invention(s) to be distinguished from other materials**. This is an important consideration since, as stated in MPEP 2163 II. A. 2., quoting the Court in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991): *"it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it*

from other materials, and to describe how to obtain it." **In summary, for the reasons given above, the applicants respectfully submit that the claims meet the Written Description Requirement of 35 USC 112, 1st paragraph.**

Rebuttal of the rejection of the applicants' arguments regarding unexpected results

The Examiner rejected the evidence the applicants cited that the claimed invention(s) achieve unexpected results, see *Response to Arguments* in the Final Rejection, p. 10. More specifically, the Examiner states that the evidence cited in the Amendment/Response of 3/10/2009 *"constitutes mere argument,"* because the evidence cited (e.g., the Equation on p. 40 and Table 2 on p. 41) *"merely compares data for different parameters."* The Examiner states: *"There is no evidence provided that compares applicant's power studies using bi-allelic markers with lower minor allele frequencies with those of the closest prior art."*

In the second paragraph under *Response to Arguments*, the Examiner indicates he has considered the *"Applicant's arguments [p.30-35] that conventional art shows highest heterozygosity gives the highest power (m=0.5), whereas the instant invention shows the highest heterozygosity gives the lowest power…."* And the Examiner states: *"The instant claims do not recite any limitations drawn to determining the highest heterozygosity or lowest power."*

Rebuttal

The applicants respectfully disagree with the Examiner that no actual evidence of unexpected results was cited in the Amendment/Response of 3/10/2009. However, in order to clarify the arguments filed on 3/10/2009, the applicants hereby make the following further remarks.

As the applicants will explain in more detail below, the Amendment/Response of 3/10/2009 contains more than reference to parameters, there are actual power calculations cited by the applicants in the arguments filed on 3/10/2009.

The Amendment/Response of 3/10/2009, refers heavily to the inventor R. E. McGinnis's published academic paper in the Annals of Human Genetics (1998) vol 62, pp. 159-179, (abbreviated as AHG98). (See for example pp. 27, 31-34, 48, 50, 73-74 of the Amendment/Response of 3/10/2009.) As noted in the arguments of the Amendment/Response of 3/10/2009, AHG98 is an academic paper in the art of linkage studies and is published in a prestigious refereed academic journal (see pp. 32, 33 & 34). **<u>Again, repeating the arguments of 3/10/2009, AHG98 contains actual power calculations, especially in Tables 1-3 on pp. 165 & 167.</u>** A copy of AHG98 was supplied as Reference A in an Information Disclosure Statement (IDS) filed in November 2000 for parent application 09/623,068. **<u>A copy of AHG98 was also supplied in May of 2008 in the file for the present application.</u> The sentences in the next paragraph regarding the power calculations in AHG98 are taken directly from p. 33 of the Amendment/Response of 3/10/2009.**

"This published paper (AHG98) includes calculations (including power calculations) in Tables 1-3, pp. 165 & 167. The calculations in these tables support major finding (2) ***including the inventor's discovery of the importance of the similarity of disease (or trait-causing) allele and marker allele frequencies for the power of association-based linkage tests.*** *As in the patent application(s) marker allele and disease allele frequencies are denoted "m" and "p" respectively and disequilibrium (or association) is given in terms of $\delta = \delta_{max}$ or $\delta = 1/2\delta_{max}$ in these Tables 1-3. As in the patent application(s) low frequency examples of "m" and "p" are given in Tables 1-3, pp. 165 & 167 of AHG98."*

The power calculations in Tables 1, 2 & 3 assume additive mode of inheritance and are for penetrance ratios 2, 4 and 10 respectively. The power calculations in these tables are fairly representative of the entire genetic parameter space. As noted at the bottom of page 164 of AHG98, *"Penetrance ratios of r = 2, 4 and 10*

were chosen as being somewhat representative of the entire genetic parameter space since I have found that P_t and P_s increase rapidly as r increases from 2 to 6 with smaller, asymptotic increases in P_t and P_s for $r > 10$. Furthermore, additive mode of inheritance may also be regarded as being somewhat representative since results from other modes of inheritance do not, in general, substantially differ from results presented here."

The power calculations in AHG98 allow the comparison of power for bi-allelic markers with lower minor allele frequencies with power for bi-allelic markers with higher minor allele frequencies. These bi-allelic markers with higher minor allele frequencies (e.g., near m = 0.5) are favored for use in linkage studies by the conventional art.

Contrary to the Examiner's statement in the Final rejection quoted above, there are power studies in AHG98 for markers with lower minor allele frequencies. Especially relevant are the TDT power calculations in each of Tables 1, 2 and 3 when the disease (minor) allele frequency p = 0.15 and marker (minor) allele frequency m = 0.50 or m = 0.25 for each of $\delta = \delta_{max}$ and $\delta = ½\ \delta_{max}$. Those TDT power results from AHG 98 for penetrance ratios r = 2, 4 & 10 from Tables 1, 2 and 3 are given below in three small Tables.

TDT power for r = 2, and values of m and δ

	$\delta = \delta_{max}$	$\delta = ½\ \delta_{max}$.
m = 0.5	0.32	0.11
m = 0.25	0.67	0.23

TDT power for r = 4, and values of m and δ

	$\delta = \delta_{max}$	$\delta = ½\ \delta_{max}$.
m = 0.5	0.96	0.53
m = 0.25	0.99	0.86

TDT power for r = 10, and values of m and δ

	$\delta = \delta_{max}$	$\delta = ½\ \delta_{max}$.
m = 0.5	0.99	0.91
m = 0.25	0.99	0.99

A comparison of the TDT power results in these above tables, clearly show that when p, the frequency of the sought, associated disease (or trait-causing) allele, is low (e.g., 0.15), then the power results for a bi-allelic marker with a lower minor (or "least common") allele frequency (e.g, 0.25) gives a significantly higher power than for a bi-allelic marker with a higher minor allele frequency (e.g., 0.5). This is especially true for lower values of the penetrance ratio, "r." Higher minor allele frequencies (e.g. near 0.5) are equivalent to higher heterozygosities (for bi-allelic markers) and these higher minor allele frequencies & heterozygosities are ironically those most favored by the conventional art. **These results were unexpected around the time of filing.**

The power results in Tables 1-3 lead to major finding (2) of AHG98. The major findings of the AHG98 are given on the second page, page 160. Major finding (2) (emboldening added) of the author/inventor's investigation is: *"(2) TDT power is increased by disequilibrium between a bi-allelic marker and disease locus,* ***and is also markedly increased when the disease allele and positively associated marker allele have similar population frequencies."*** **This major finding leads to the inventor's advocating the use, for example, of bi-allelic markers with lower minor allele frequencies such as 0.3, 0.2 and 0.1 in linkage studies whose target disease (or trait-causing) polymorphism has a lower allele frequency, such as p = 0.15 (or p = 0.1). This major finding is based on all the power calculation results in Tables 1, 2 & 3, not just on the results in the three small tables for p = 0.15 given above. Again, major finding (2) of the author/inventor's investigation is in a published paper in a prestigious refereed academic journal.**

To quote from the bottom of p. 166 of AHG98 (emboldening added): *"In concluding this section, I emphasize that Tables 1-3 show that when the disease locus and marker are bi-allelic,* ***TDT power is substantially increased if the disease allele and positively associated marker allele have similar frequencies.*** *...... For example, in Table 3 (r = 4), note that when $\delta = ½\,\delta_{max}$. and p = 0.15, a similar frequency (m = 0.25) for the disease-associated marker allele produces TDT power of 0.86 and P_t of 0.581; but when p=0.15 and m=0.5 at $\delta = ½\,\delta_{max}$, TDT power and P_t fall to 0.53 and 0.547, respectively. The difference in TDT power for these two situations can also be quantified by calculating the mean value of χ^2 tdt based on a sample of 200 ASP families and the values of P_t and H/F in Table 4 [i.e. χ^2 tdt = 800(H/F) (2 P_t -1)^2]. When p = 0.15 and m = 0.5, χ^2 tdt =3.53 yielding a significance level of p = 0.06; but when p = 0.15 and m = 0.25, χ^2 tdt = 9.02 for a significance level of p < 0.003."*

As noted above, TDT power for two situations can also be quantified by calculating the mean value of χ^2 tdt [i.e., χ^2 tdt = 800(H/F) (2 P_t -1)^2] based on a sample of 200 ASP families and the values of P_t and H/F. **This power comparison using χ^2 tdt calculations is given in the instant patent application on p. 43 lines 17 to 24 (PCT p. 42 lines 17 to 24).** That comparison shows that TDT power when r = 5, $\delta = ½\,\delta_{max}$., and p = 0.1 for m = 0.5 yields χ^2 tdt with a significance level of p < 0.1. But when m = 0.2 (a lower minor allele frequency which is closer to p = 0.1) the χ^2 tdt calculation yields a significance level of p < 0.005, equivalent to a much higher power. **Again, this calculation is an actual comparison of power, comparing TDT power for a lower minor allele frequency (m = 0.2) with a higher minor allele frequency (m = 0.5). As noted above, higher minor allele frequencies (e.g. near 0.5) are equivalent to higher heterozygosities (for bi-allelic markers) and these higher minor allele frequencies & heterozygosities are <u>ironically</u> those most favored by the conventional art. Higher minor allele frequencies (e.g. near 0.5) are**

equivalent to higher heterozygosities (for bi-allelic markers) and these higher minor allele frequencies & heterozygosities are <u>ironically</u> those most favored by the conventional art. These results were unexpected around the time of filing.

For the Examiner's convenience, the applicants now reproduce a paragraph about the correlation between minor allele frequency and heterozygosity from p. 30 of the Amendment/Response of March 10, 2009. *"For the Examiner's convenience the heterozygosity of a bi-allelic marker is, as stated in Cohen (1997) at col. 11 lines 6-8, 2 P_a (1- P_a), where P_a is the frequency of allele a. So for the heterozygosities for bi-allelic minor allele frequencies are as follows: P_a =0.1, Heterozygosity=0.18 or 18%; P_a =0.2, Heterozygosity=0.32 or 32%; P_a =0.3, Heterozygosity=0.42 or 42%; P_a =0.4, Heterozygosity=0.48 or 48% and P_a =0.5, Heterozygosity=0.5 or 50%.* ***Thus bi-allelic markers with the highest minor allele frequency of 0.5 have the highest heterozygosity. And bi-allelic markers with low minor allele frequencies, e.g., 0.1, have low heterozygosities.****)"* Cohen (1997) is U.S. Patent 5,945,522 filed Dec. 22, 1997 and cited as a reference by the Examiner in the Rejection of 9/22/08.

<u>Further evidence that the power of association-based linkage studies depends on marker allele frequency. And further evidence that power for bi-allelic markers with lower minor allele frequencies is higher for bi-allelic markers with higher minor allele frequencies in some situations. This was an unexpected result around the time of filing. Bi-allelic markers with higher minor allele frequencies (e.g., near m = 0.5) are favored for use in linkage studies by the conventional art.</u>

The applicants now cite further evidence of "unexpected results" for bi-allelic markers with lower minor allele frequencies. This evidence is from a paper in the published academic literature. More specifically, we have included a copy of Wray N (2005) *Twin Research & Human Genetics* 8:87-94 with the present

Response. This published academic paper explores the impact of the relative allele frequencies of a causal allele (such as a disease or trait-causing allele) and a marker allele on the power of association studies. This Wray paper includes actual power calculations, e.g., see Figure 3 p. 92. The conclusion of this Wray paper is very similar to major finding (2) in the inventor's paper AHG98 (that major finding is that TDT power is increased when the disease (or causal) allele and positively associated marker allele have similar population frequencies). More specifically this Wray paper concludes that to detect association with a reasonably high degree of power (e.g., 80 % or 60%), the maximum allele frequency difference between the causal allele and associated marker allele is 0.06; see p. 93, bottom of left column. This means, of course, that to detect lower frequency causal alleles such as $p = 0.15$ or $p = 0.1$, the most powerful markers have marker allele frequencies (m) with lower values, i.e., $m \leq 0.21$ or $m \leq 0.16$ respectively (and even more specifically $0.09 \leq m \leq 0.21$ or $0.04 \leq m \leq 0.16$ respectively).

The applicants have presented evidence above that the claimed invention(s) have the property of being useful to help detect trait-causing alleles with lower minor allele frequencies. The evidence cited above includes actual power calculations.

The following quote is from pp. 18 & 25 of the Amendment/Response of March 10, 2009 and is still valid. *"These whereby clauses delineate groups or subsets (or subgroups) of lower minor allele frequency (lower heterozygosity) covering markers that have the unexpected, unobvious property of increased power to detect linkage in association studies. More specifically the increased power is to detect linkage (in association studies) to lower frequency trait-causing polymorphism alleles, such as a disease allele with a low allele frequency "p," p = 0.1."* (We have also presented evidence above using another low frequency example of $p = 0.15$.)

As recited in the pending claims, the claimed inventions have *"utility to determine genotype data or sample allele frequency data for each of the two or more covering markers."* This genotype data or sample allele frequency data has utility in the association linkage studies described in the above paragraph, that have the property of increased power to detect lower frequency trait-causing polymorphism alleles. **Thus the claimed inventions have the property of being useful (i.e., having increased power) to detect linkage (in association studies) to lower frequency trait-causing polymorphism alleles.**

As argued briefly here and more extensively in the Amendment/Response of March 10, 2009, this property is unexpected & unobvious. If the Examiner is stating that these arguments are moot (p. 10 of the Final Rejection), then the applicants respectfully disagree, especially in light of the evidence presented above.

The applicants respectfully submit that the information given just above about the (unexpected) property of the claimed inventions is a response to the contention the Examiner is making in the second paragraph under *Response to Arguments* of the Final Rejection. More specifically in the second paragraph under *Response to Arguments* of the Final Rejection, the Examiner indicates he has considered the *"Applicant's arguments [p.30-35] that conventional art shows highest heterozygosity gives the highest power (m=0.5), whereas the instant invention shows the highest heterozygosity gives the lowest power…."* And the Examiner states: *"The instant claims do not recite any limitations drawn to determining the highest heterozygosity or lowest power."*

Regarding the sentence just above, the pending claims **<u>do recite limitations drawn to markers (and complementary oligonucleotides) with a property of increased power</u>**. Each instant claim contains a "whereby clause" which is a result of these claim limitations. To repeat what is above and re-quote from the

Amendment/Response of March 10, 2009, *"These whereby clauses delineate groups or subsets (or subgroups) of lower minor allele frequency (lower heterozygosity) covering markers that have the unexpected, unobvious property of increased power to detect linkage in association studies."*

Conclusion

The applicants have responded to rejections in the Final Office Action of 10/20/2009 by amending claim 91. No new claims were added for a total of 76 pending claims, unchanged from the previous total. A fee for an RCE and a small entity two-month extension fee under 37 CFR 1.136(a) is paid, or will be paid separately.

The applicants have addressed the objection to the Specification by requesting an amendment of the Specification. The applicants have addressed Rejections of the claims for failure to meet Priority requirements by (1) citing support for the claims in the PCT parent and also by (2) addressing the part of this rejection, failure to meet the Requirements of 35 USC 112, 1st paragraph (including citing corresponding passages in the PCT parent). The applicants have addressed Rejections of the claims for failure to meet the Requirements of 35 USC 112, 1st paragraph (lack of enablement and failure to meet the Written Description Requirement) by presenting remarks and arguments that the claims do indeed meet the Requirements of 35 USC 112, 1st paragraph. These remarks and arguments also cite corresponding passages in the PCT parent.

The applicants have addressed rejection of the claims for indefiniteness by amending claim 91. The applicants have addressed rejections of the claims for failure to provide evidence of unexpected results, by making remarks and arguments that the claimed invention(s) do indeed achieve unexpected results. Further remarks regarding previously presented evidence and arguments were made and new evidence was also presented.

For the reasons advanced above, applicants respectfully submit that the claims are now in condition for allowance and that action is earnestly solicited.

Respectfully submitted,

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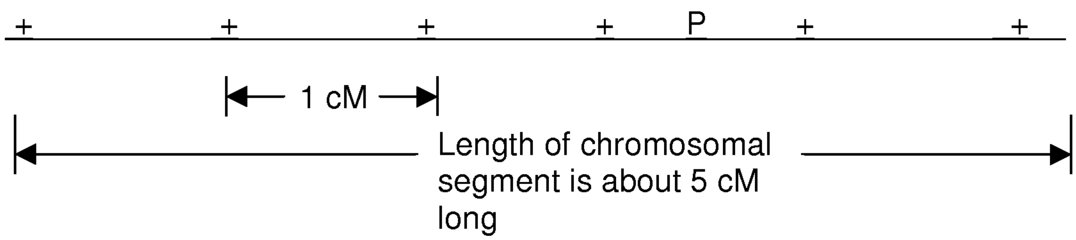
Attachments: Diagrams 1 & 2, page 45

Attached Non-patent literature (NPL): Wray N (2005) *Twin Research & Human Genetics* 8:87-94

Diagram 1

Diagram 1 shows the chromosomal locations of six markers in a conventional essentially one-dimensional scan



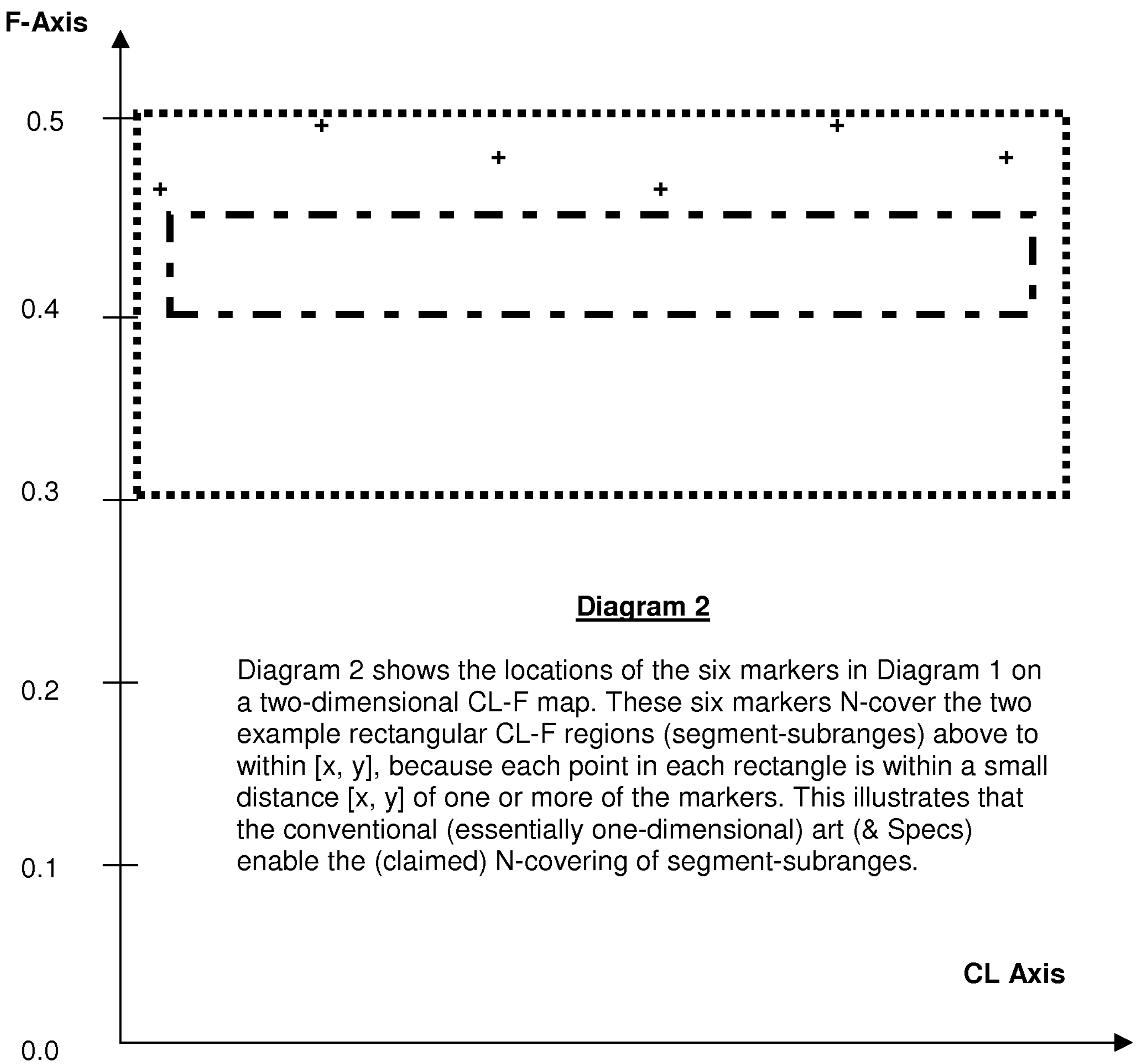


Diagram 2

Diagram 2 shows the locations of the six markers in Diagram 1 on a two-dimensional CL-F map. These six markers N-cover the two example rectangular CL-F regions (segment-subranges) above to within [x, y], because each point in each rectangle is within a small distance [x, y] of one or more of the markers. This illustrates that the conventional (essentially one-dimensional) art (& Specs) enable the (claimed) N-covering of segment-subranges.